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Agranulocytosis and Antithyroid Drugs

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Propylthiouracil and methimazole are used widely in the treatment of hyperthyroid disorders. The most important complication of the use of these drugs is depression of the neutrophilic granulocyte count. Granulocytopenia occurs in about 4 percent and agranulocytosis occurs in about 0.3 percent of treated patients. Although this depression of the granulocyte count is reversible after the drug is discontinued, serious infection frequently accompanies agranulocytosis and accounts for almost all deaths related to the drugs. It is important to be aware of the clinical features of granulocytopenic reactions due to antithyroid drugs.

THE TYPES OF TREATMENT used for the various forms of hyperthyroidism include surgical operation, radioactive iodine and antithyroid drugs. The thiourea derivatives, among which are included thiouracil, methylthiouracil, carbimazole, methimazole and propylthiouracil, have, in addition to radioactive iodine, provided the principal mode of nonsurgical treatment for hyperthyroidism since the institution of their use about 30 years ago. The efficacy of propylthiouracil[1-4] and methimazole[5-7] has been well established. These are the two antithyroid agents in widest use in the United States today, largely because of the relatively low incidence of side effects compared with other agents such as thiouracil.[8-10]

In spite of the efficacy and relative safety of propylthiouracil and methimazole, there are adverse reactions. Among the common adverse effects are skin rashes, urticaria, drug fever and arthralgias.[11] Submaxillary gland enlargement and lymphadenopathy may develop.[12] Hypothyroidism may result if the dosage of drug is not reduced when hyperthyroidism comes under control.[4] Rarely cholestatic jaundice occurs and may be prolonged up to several months.[13-19] Rare lupus-like syndromes include skin ulcers,[20] splenomegaly,[20,21] migratory polyarthritis,[22] pleuritis and pericarditis,[23,24] periarteritis[25] and renal abnormalities.[11,21] Serologic abnormalities include hyperglobulinemia,[11,23] positive lupus erythematosus (LE) cell preparations[11] and the presence of antinuclear antibodies.[11,21,22] Rare hematologic complications of therapy are aplastic anemia,[26-31] pure red cell aplasia[27] and thrombocytopenia.[7,14,16,27]

By far the most frequent adverse hematologic effect of antithyroid drugs, however, and the one of most concern for physicians and patients, is granulocytopenia.[8-16,23,32-45] Most of the common adverse effects have minor significance, and the potentially serious problems of liver involvement

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and lupus-like syndromes are very rare. Agranulocytosis is relatively common, however, affecting about one in 300 patients receiving methimazole or propylthiouracil.[10] It is often accompanied by serious infection and accounts for most of the reported drug related deaths. This paper reviews the clinical features of granulocytopenic reactions due to antithyroid drugs.

Incidence

The terms "granulocytopenia" and "agranulocytosis" are not rigidly defined in the literature, but in general they refer to neutrophilic granulocyte counts in the peripheral blood of less than 1,500 per cu mm and 250 per cu mm, respectively.

There is no apparent age predilection for granulocytopenia induced by antithyroid drugs. Children and adults both are affected. Although the case incidence is higher in females, this probably reflects the higher incidence of hyperthyroid conditions in this group and the resultant exposure to these drugs.[38]

None of the thiourea derivatives have been free of the complication of granulocytopenia. Although thiouracil was an extremely effective antithyroid agent, the primary reason for its discontinuation was the high incidence of granulocytopenic reactions. Van Winkle and co-workers[33] collected reports of 5,745 cases of hyperthyroidism treated with thiouracil and found a 4.4 percent incidence of leukopenia and a 2.5 percent incidence of granulocytopenia. A similar complication rate was noted in the 1,914 thiouracil-treated patients reviewed by Sikkema and associates[37] and the 1,091 patients in Moore's review.[9] Of these 3,005 patients,[9,37] 20 of 63 patients in whom agranulocytosis developed, died, for an overall 0.67 percent chance of death from thiouracil therapy. Clearly, safer alternatives were necessary.

It was felt that propylthiouracil would be an ideal answer when early trials by Astwood and co-workers[1] and McGavack and associates[3] totaling 175 patients failed to show any leukopenic reactions. However, McCullagh and co-workers[34] noted a case among their 110 patients, and subsequently Bartels[39] published his report of 672 patients treated preoperatively with propylthiouracil among which there were seven instances of granulocytopenia and three cases of agranulocytosis. Beebe and co-workers[41] reported on 1,651 collected cases with 19 instances of granulocytopenia and one case of fatal agranulocytosis. McGavack and Chevalley[10] reviewed the subject of leukopenic reactions due to propylthiouracil and methimazole. They found no reactions in patients receiving less than 25 mg of methimazole per day but a 5.4 percent incidence of decreased granulocyte count in those taking 30 mg or more, with one death in about 900 patients. Among the 931 propylthiouracil-treated patients, there was a 2.8 percent incidence of granulocytopenia in those taking less than 150 mg a day, and a 4.5 percent rate in those taking more than 250 mg a day, with one death. The authors concluded that equally effective doses of propylthiouracil and methimazole had a similar rate of complication with a 0.1 percent risk of death due to therapy, and that there was a relationship between dose and risk of granulocytopenia. This relationship was also noted by Wiberg and Nuttall[45] who noted two cases of agranulocytosis among 25 patients receiving 120 mg methimazole per day.

Clinical Features

The clinical features of agranulocytosis due to antithyroid drugs are similar among the various agents. The onset of symptoms is usually abrupt. The commonest presenting complaints are fever, malaise, gingivitis and sore throat. Those patients with granulocytopenia without agranulocytosis usually remain asymptomatic. The alarming suddenness with which symptoms of agranulocytosis may develop is well known;[37] granulocytes may disappear from peripheral blood over two days.[32] Leukopenia may be noted before the development of agranulocytosis.[9,15,36,37] When agranulocytosis develops it generally does so within the first few months of therapy.[10,13,14,35,38-42] It may occur as early as ten days after therapy is begun[10] or may be delayed for up to four months or more.[38,40] Moreover, in patients who previously tolerate a drug well agranulocytosis may develop after repeat courses of therapy with the same drug.[13,36]

The course of symptomatic agranulocytosis may be fulminant with death due to infection occurring within several days.[14,40,41] In patients who recover following discontinuation of the drug, granulocytes reappear in the peripheral blood after a period varying from a few days to three weeks, and the granulocyte count returns to normal shortly thereafter.[8,10,35,38,39,42,46] The course of aplastic anemia due to antithyroid drugs may be prolonged.[29,30]

Among detailed case reports of 25 patients in whom severe drug-related granulocytopenia developed,[8,9,13-16,35,36,38-43,45] other simultaneously oc-

curring drug-induced side effects were infrequently noted. In one patient urticaria was present,[36] in one generalized lymphadenopathy and splenomegaly occurred[8] and in four jaundice developed.[14-16,44]

Bone Marrow

There are no unique diagnostic changes in bone marrow in cases of agranulocytosis due to antithyroid drugs.[12,14,26,29-31,35-37,41-43,45] Except in the rare instances of pancytopenia which are accompanied by an aplastic marrow, only the granulocyte line is affected. The relative number of granulocytes and their precursors may vary considerably from apparent absence to hyperplasia, although a decrease is most common. The marrow morphology is likely to reflect the time during the clinical course at which the specimen is taken.[46] The distribution of granulocytes is frequently "left-shifted," and the appearance of "maturation arrest" is common. Among the 14 studied cases of thiouracil-induced agranulocytosis collected by Sikkema and associates,[37] features compatible with maturation arrest were seen in five. Whether or not the appearance of the marrow in these cases truly represents a maturation arrest is unknown. Excessive utilization of a small pool of granulocyte precursors may produce features of maturation arrest. Moreover, injury incurred at an early stage of granulocyte differentiation may possibly give the appearance of arrest of maturation at a later stage of development.[47] The stage of granulocyte development at which injury is induced by the thiourea derivatives is not known. In a single case[41] a peroxidase stain showed no positive staining cells, suggesting that the defect was imposed at the myeloblast stage or earlier. Morphologic changes have been noted in mature granulocytes[36,43] consisting of cytoplasmic swelling with indistinct margins, and irregularly staining, pyknotic nuclei. The significance of these latter findings is unclear.

Pathogenesis

Information available that might shed some light on the pathogenesis of the granulocytopenia and agranulocytosis related to antithyroid drugs is scanty, and the fundamental questions regarding its mechanism are unanswered. The effect of antithyroid agents on thyroid hormone metabolism has been intensively studied. The most important antithyroid actions are to inhibit the oxidation of iodide to the iodinating species necessary in the synthesis of iodotyrosines and to inhibit the formation of iodothyronines from the coupling of iodotyrosines.[48] Much less is known about the extrathyroidal effects, and specifically the effect on the bone marrow.

Thiouracil readily gains entry into marrow tissue. Its level builds up slowly and eventually exceeds concentrations in the thyroid.[49] In patients with nonthyroidal conditions who were given large doses of thiouracil, high concentrations were found in the marrow.[50] Drug levels within leukocytes may be several times that of plasma.[49]

Oxygen and glucose utilization by leukocytes is affected. Granulocytes from propylthiouracil-treated rats are found to be hypermetabolic with increased oxygen and glucose utilization especially during phagocytosis, an effect independent of thyroid status.[51] However, control leukocytes incubated *in vitro* with propylthiouracil do not show any change in glucose utilization through a wide range of propylthiouracil concentrations.[51] An apparently conflicting observation is that it is possible to show a small but significant decrease in oxygen consumption in granulocytes and to a lesser extent in erythroid cells in the presence of high concentrations of thiouracil.[52]

Very few specific enzymes have been studied in relation to the thiourea derivatives. The cytochrome oxidase activity of thyroid tissue is inhibited by 0.002 mol of thiouracil *in vitro;* however, concentrations up to 0.01 mol do not affect bone marrow[53] although higher concentrations may be inhibitory, raising the question of the significance of the dosage-time factor in some metabolic systems.[37] Leukocytes treated with propylthiouracil show slight decreases in the activity of soluble nicotinamide adenine dinucleotide, reduced form (NADH) oxidase, granule bound nicotinamide adenine dinucleotide phosphate, reduced form (NADPH) oxidase and NADH lactic dehydrogenase.[51] The significance of the preceding observations regarding the development of agranulocytosis is unknown.

Some observations regarding the effect of these agents on nucleic acid metabolism have been made. Thiouracil interferes with ribonucleic acid (RNA) synthesis in slices of rat liver and thymus.[54] Most interesting is that uracil can reverse the inhibition of reticulocyte maturation by thiouracil *in vitro,* suggesting thiouracil is an antimetabolite which may be overcome by adequate concentrations of a necessary substrate.[55] Seemingly contrary to the above is the report that orotic acid

incorporation into RNA of young leukocytes in propylthiouracil-treated rats is increased.[51] However, the same increase is noted in thyroidectomized animals, and therefore this observation may reflect the thyroid state of the animal rather than the effect of propylthiouracil. In one case of marrow aplasia in man due to propylthiouracil,[28] there was no effect of the drug on incorporation of formate or orotic acid into deoxyribonucleic acid (DNA) or RNA, or on uptake of leucine into protein in the bone marrow after recovery.

Specific antibodies are rarely shown. In two cases of aplastic anemia,[28,30] no leukoagglutinins or platelet agglutinins were found. In a patient with propylthiouracil-induced leukopenia, skin ulcers, fever, arthritis, splenomegaly and hyperglobulinemia,[20] immunofluorescent studies with antihuman globulin suggested the presence of an antibody directed to granulocyte cytoplasm. Serum from the patient agglutinated donor granulocytes, and the agglutination was less pronounced with previous incubation of the serum with propylthiouracil. It was suggested that in this patient there was a hypersensitivity disorder with autoimmune leukopenia related to propylthiouracil administration. However, in most cases of granulocytopenia associated with thiourea derivatives, no clinical features suggesting a hypersensitivity disorder are seen. It is likely that agranulocytosis due to antithyroid drugs is not antibody mediated.

Any proposed mechanism relating granulocytopenic reactions to antithyroid drugs will have to take into consideration some clinical observations. First, in only a small percentage of exposed persons does granulocytopenia develop, and even in fewer is there the severe degree of agranulocytosis. Second, the onset of granulocytopenia is frequently delayed. Third, the incidence increases with higher doses. And last, the granulocyte line is usually the only one affected. At present, it seems probable, as previously suggested,[28] that in some persons there is a biochemical susceptibility involving some essential metabolic pathway.

Prevention and Treatment

Unfortunately, there is no way to predict in which patient drug-associated agranulocytosis will develop. It is not clear that following blood counts aids in management since agranulocytosis may develop swiftly. Hence it is most important that patients be warned to discontinue medication and contact their physicians if fever, gingivitis or sore throat develops. Agranulocytosis is usually not presaged by other drug related side effects such as rash, urticaria or arthralgias. Conversely, there is no evidence that patients in whom side effects do develop have an increased risk of developing agranulocytosis.

The proper approach to patients in whom mild to moderate granulocytopenia develops is not clear. In some patients no further depression of the granulocyte count may ever occur and there may be resolution of granulocytopenia despite continued therapy. Amrhein and co-workers[11] reported several patients with propylthiouracil-induced granulocytopenia, and the leukopenia resolved with continued treatment. In half the patients with thiouracil-induced leukopenia reported by Van Winkle and associates,[33] the leukocyte count returned to normal levels in spite of continued therapy. A patient with agranulocytosis due to thiouracil was subsequently given the drug again without complication.[32] Granulocytopenia may be associated with hyperthyroidism, and in these instances the granulocyte count may rise with antithyroid therapy.[45]

Very little information is available concerning the safety of changing therapy to another thiourea derivative in patients with granulocytopenic reactions. In a few patients in whom granulocytopenia developed with propylthiouracil administration, there was no improvement in the leukocyte count with thiouracil or methimazole therapy.[11,38] Two patients who had propylthiouracil-induced agranulocytosis were subsequently given thiouracil. In one, agranulocytosis developed; in the other it did not.[39] Patients may tolerate one or more drugs well and yet a severe reaction to another may develop. A patient with methimazole-induced aplastic anemia had had previous exposure to propylthiouracil with only an urticarial reaction.[26] Another patient was treated with thiouracil for 3 months and with methylthiouracil for 21 months, and then fatal marrow aplasia developed after carbimazole was given for 4 months.[27] Unfortunately, there are inadequate numbers of reported cases and no controlled studies concerning the safety of continued therapy with antithyroid drugs in the presence of granulocytopenia. It would seem wise, however, to be certain of the indication for continued medication, to reduce the dose to the minimum necessary to control hyperthyroidism and to follow blood counts in patients who have significant granulocytopenia.

Once agranulocytosis with overt infection is established, treatment consists of immediate ad-

mission to hospital, discontinuation of the drug, specific antimicrobial therapy, treatment of hyperthyroidism and general supportive measures. Isolation techniques and granulocyte transfusions may be beneficial. In survivors, the granulocyte count will usually return to normal levels in a period varying from a few days to three weeks.

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